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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/760,085	01/16/2004	Hubert Koster	119368-00025 / 2309	8019

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EXAMINER
LIU, SUE XU

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
07/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/760,085	KOSTER ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/08;8/28/08;5/27/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,5,6,10,15,17,18,22,25,34,38,43,44,46,47,55,56,63,66-68,75,77,110,116,137,139,140,143-147,151-153,155,156,158-161,163,164,166-169,171,172 and 174.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 5,17,18,22,44,46,47,55,56,63,66-68,77,143,145-147,153,155,156,167,168,171,172 and 174.

Continuation of Disposition of Claims: Claims rejected are 1,2,6,10,15,25,34,38,43,75,110,116,137,139,140,144,151,152,158-161,163,164,166 and 169.

DETAILED ACTION

Please note the change of examiner for this application. (Please see the Conclusion paragraph for information on any future correspondence.)

Status of the Claims

1. Claim 173 has been added.

Claims 3, 4, 7-9, 11-14, 16, 19-21, 23, 24, 26-33, 35-37, 39-42, 45, 48-54, 57-62, 64, 65, 69-74, 76, 78-109, 111-115, 117-136, 138, 141, 142, 148-150, 154, 157, 162, 165, 170 and 173 have been cancelled.

Claims 1, 2, 5, 6, 10, 15, 17, 18, 22, 25, 34, 38, 43, 44, 46, 47, 55, 56, 63, 66-68, 75, 77, 110, 116, 137, 139, 140, 143-147, 151-153, 155, 156, 158-161, 163, 164, 166-169, 171, 172 and 174 are currently pending.

Claims 5, 17, 18, 22, 44, 46, 47, 55, 56, 63, 66-68, 77, 143, 145-147, 153, 155, 156, 167, 168, 171, 172 and 174 have been withdrawn.

Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are being examined in this application.

Election/Restrictions

2. Applicant's election of Group I (i.e., claims 1, 2, 5, 6, 10, 15, 17, 18, 22, 25, 34, 38, 43, 44, 46, 47, 55, 56, 63, 66-68, 75, 77, 110, 116, 137, 139, 140, 143-147, 150-153, 155-161, 163, 164, 166-169, 172, and 173) **with traverse** is as previously acknowledged.

3. Applicant's election of species **with traverse** is also as previously acknowledged.

Information Disclosure Statement

4. The information disclosure statements filed 5/15/08, 8/28/08 and 5/27/09, fail, in part, to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because of a copy of the indicated references was not provided and/or the author of the indicated references was not provided. See the attached PTO-1449 for indications of the non-considered references.

5. The references listed on applicant's PTO-1449 forms have been considered by the Examiner (except where indicated). A copy of the form is attached to this Office Action.

Specification

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Priority

7. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The present application claims benefit to 60/441,398 filed 1/16/2003 (referred to herein as '398).

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

However, '398 fails to provide adequate support under 35 U.S.C. § 112, first paragraph for the claimed invention as follows:

(A) For ***claim 152***, '398 fails to provide support for X = diazirine.

(B) For ***claim 166***, '398 fails to provide support for determining the function of the biomolecule by pharmacophore, homology models, back-mapping to yeast pathways, simulations, knock-out/knock-in, prospective genotyping, etc.

If applicant believes this assessment is in error, applicant must disclose where in the specification support for these limitations can be found. Therefore, the earliest effective filing date for claims 152 and 166 and all dependent claims is the filing date of the case **January 16, 2004**. All other claims are afforded a priority date **of January 16, 2003** for 60/441,398.

Claim Objection(s) / Rejection(s) Withdrawn

8. All previous claim Objection(s) / Rejection(s) as set forth in the previous Office action (mailed 11/15/07) that are not repeated and/or maintained in the instant Office action are withdrawn.

Claim Objection(s) / Rejection(s) Maintained

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A.) **Claim 1** recites "identifying targets and non-targets of a drug" and "wherein the captured biomolecules comprise drug targets and non-targets", which recitations are unclear and render the said claim indefinite. The instant claims seem to recite conflicting limitations. It is not clear how a compound/molecule can be both a drug target as well as a non-target simultaneously. The instant claim 1 seems to recite due both of the "drug target" and the "non-targets" are identified by binding or bonding to the capture compound. Thus, it is not clear how a single function of "binding" can lead to opposite results of a target and a non-target.

B.) **Claims 1 and 2** recite the term "non-targets" or drug non-targets, which term seems to be in conflict with the method steps of the instant claim 1. The instant specification defines the term "drug non-target" as "a biomolecule, such as a protein including but not limited to receptors and enzymes, that the drug is **not** intended to interact with in vivo." However, the instant claimed method requires the biomolecules "interact" (bind) with the capture molecule through

the "drug" (i.e. "biomelecule(s) in the sample that interact with Y"). Thus, the term "drug non-target" conflicts with the required method step of "interact" with the drug.

C.) **Claim 163** recites the limitation "the mass spectrometry format" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 164 and all dependent claims are rejected under 35 USC 112, second paragraph.

D.) **Claim 164** recites the limitation "the detection form" in line 1. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 164 and all dependent claims are rejected under 35 USC 112, second paragraph.

Discussion and Answer to Argument

11. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the claim amendments have overcome the above rejections. (Reply, pp.14+).

The claim amendments have elicited new issues as discussed above. In addition, the rejections regarding the instant claims 163 and 164 have not been overcome. It is suggested the instant claim 110 be amended to recite "by mass spectrometry"; the instant claims 163 and 164 be amended to recite "wherein the mass spectrometry is selected from…"

Claim Rejections - 35 USC § 112, first paragraph

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description rejection

13. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

Applicant's claims are directed to a broad genus of methods for isolating and identifying biomolecules that have been "captured" by a capture compound of formula Q-Z-$(Y/X)_{n/m}$. The Q moiety is described as a sorting function. Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug. X is a ligand to a biomolecule that binds with sufficiently high affinity so that it will be "stable" under mass spectrometric analysis. And Z is moiety for presenting X, Y and Q. Thus, the claims encompass virtually an infinite number of methods employing virtually an infinite number of capture compounds because no structural limitations have been set forth. That is, Applicants have not limited the number of atoms, types of atoms, or the manner is way said atoms can be connected in defining the Q, X, Y and Z moieties. They could be composed of any element in the periodic table. Furthermore, the dependent claims also fail to limit at least one of the X, Y, Z, and Q moieties to anything less than an infinite number of possibilities. Thus, Applicant's claims encompass the entire universe

of drugs, drug fragments, drug metabolites, sorting functions, ligands, etc. without exception.

In contrast, Applicants set forth only a handful of examples in their specification that have been used to capture compounds under "equilibrium" conditions. For example Q could be biotin, an oligonucleotide, hex-His, antibody, lectin, PNA, peptide(see specification, page 53, paragraph 1). No entirely "inorganic" Q sorting function is disclosed. X, according to Applicants, could be a photoactivatable group or an activated ester if used under acidic conditions (e.g., see also page 87; see also Example 15; see especially page 197, lines 5-11 describing why photoactivatable groups are required, "The central assumption is that the photolysis process is a very rapid process so that the amount of the covalently crosslinked substrate enzyme complex is directly proportional to the amount of the complex in equilibrium"; see also page 47, last full paragraph wherein an azide is presented; see also page 124, compound A for an example of such an azide; see also page 76, paragraph 1 wherein a diazirine group is disclosed and an NHS group that is "inert" under acidic pH but is subsequently activated at high pH; see also original claims 141 and 142 disclosing arylazides and phenyl azides). Although many other X groups were described in the specification, none were described as being able to capture compounds under "equilibrium" conditions. Several commonly known drugs were described for the "Y" position such as Troglitazone, Rosiglitazone, Pioglitazone (e.g., see prophetic example 16) and atorvastatin calcium i.e., LIPITOR (e.g., see specification page 91). A drug metabolite of Actos and Avandia were also described (e.g., see specification, pages 206 and 207). No example of a drug "fragment" is provided that could read, quite literally, on a single carbon atom. No example of a "prodrug" is provided. Finally, only multivalent "carbon based" Z presenting units are provided. No inorganic examples are given (e.g., see claim 34).

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the claimed invention (e.g., see *In re Edwards*, 568 F.2d 1349, 1351-52, 196 USPQ 465, 467 (CCPA 1978); see also see also *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111 (CAFC 1991)). Furthermore, a "written description on an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). Here, Applicant has failed to provide a definition, structure, formula or chemical name for at least one of Q, Z, Y and Z describing them in most cases in entirely functional terms. In addition, the CAFC has stated that a genus, which is set forth only in functional terms, "... is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function" (e.g., see *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (1997)). Here, Applicant's claimed screening method employs molecules with Q, Z, X and Y that can only be distinguished from other compounds by their function. For example, claim Q is defined in purely functional terms (i.e., its ability to sort), which was held to be impermissible in *Lilly*. Likewise, Z is defined in terms of its ability to "present" and X is defined in terms of its ability to bind sufficiently such that it is "stable" under mass spectrometric analysis. Just as the generic term "cDNA" did not provide an adequate written description for the broad class of mammalian or vertebrate insulin DNA in *Lilly*, neither does the generic terms X, Y, Q and Z provide an adequate written description for this broad class of capturing molecules because these

terms only defines what parts of the compound does (i.e., ability to sort) rather than what it is (i.e., molecular formula such as biotin). In fact, this case is even more egregious than *Lilly* because there is no "genetic code" to correlate the structure with the function. Furthermore, such a correlation could not exist because the claim does not define what is being sorted (for Q), what the conditions for the mass spectrometric analysis are (for X), or what the metabolic/chemical conditions are being considered for the drug metabolite, drug intermediate, prodrug, and drug fragment (for Y)

In addition, when there is *substantial variation within the genus*, one must describe a sufficient variety of species to reflect the variation within the genus (e.g., see MPEP § 2163.05). Here, the variation within the genus would be enormous because the nature of the claimed invention would depend on a vast number of structurally undefined variables including Q, Z, X and Y. Any atom in the periodic table could be used. Any combination of said atoms would be permitted. The vast majority of the periodic table is "inorganic" in nature but Applicants set forth only "organic" examples for Q, Z, X and Y.

Furthermore, the general knowledge and level of skill in the art do not supplement the omitted description because no known structure/function relationship and/or chemical properties exists that could otherwise be used to show possession of the enormous genus. In addition, there is no known generally accepted method for producing the wide array of compounds used in the claimed methods (e.g., see MPEP § 2163, Factors to be considered in determining whether there is sufficient evidence of possession include "[1] the level of skill and knowledge in the art, [2] partial structure, [3] physical and/or chemical properties, [4] functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the [5]

method of making the claimed invention"). For example, as noted above, the compounds that are used in the presently claimed method could be constructed from any element in the periodic table combined in virtually an infinite number of ways. However, Lauf et al. state, "The preparation of new materials with novel and useful chemical and/or physical properties is at best unpredictable considering current levels of understanding. Consequently, the discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Given approximately 100 elements in the periodic table, which can be used to make compositions consisting of three, four, five, six or more elements, the universe of possible new compounds remains largely unexplored" (e.g., see U.S. Patent Application Pub. No. 2004/0062911 A1, page 1, paragraph 4). Thus, the presently claimed compounds by analogy "remain largely unexplored" because they could be constructed of any conceivable combination of elements in the periodic table. Furthermore, although organic chemistry (i.e., compounds restricted to a limited number of elements in the periodic table) is a mature art, it is not sufficiently developed to permit the synthesis of any pharmaceutical drug, drug fragment, drug intermediate, drug metabolite, etc. For example, Keaslin et al. state, "many natural products [which would include pharmaceutical drugs, drug fragments, drug intermediates, drug metabolites, etc.] have complex structures, and, as a result, are currently … impossible to synthesize" (e.g., see Keasling et al., US Patent Application No. 2006079476, paragraph 6).

Furthermore, it is unclear how a sufficient time for reaching equilibrium between the biomolecule and the capture compound can be achieved without the use of a photoactivatable X group or, alternatively, an X group that can be activated by a change in pH (see above). Reaching equilibrium takes time and an X group that is constitutively activated would not permit

such a waiting period. A constitutively activated X group would react immediately with the target before equilibrium could be achieved between the drug and the biomolecule. Thus, Applicants were not in possession of any X group but, rather, only a select number of "activatable" groups (e.g., see Example 15 wherein a photoactivatable group was used to take a "snap shot" of the reaction at the time of photolysis).

Thus, the claims fail to satisfy the constitutional requisite of promoting the progress of science and the useful arts since this seeks to monopolize all possible ways to achieve a given result (e.g., any sorting function, any covalent binding means), far beyond those means actually discovered or contemplated by the inventor (e.g., biotin, photoactivatable groups, etc.), so that others would have no incentive thereafter to explore a field already fully dominated. *O'Reilly v. Morse*, 15 How. 62, *In re Fuetterer*, 50 CCPA 1453, 1963 C.D. 620, 795 O.G. 783, 319 F.2d 259, 138 USPQ 217; *Siegel v. Watson*, 105 U.S. Appl. D.C. 344, 1959 C.D. 107, 742 O.G 863, 267 F.2d 621, 121 USPQ 119.

Discussion and Answer to Argument

14. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the instant claims "are directed to methods, not to compounds", and the "reagents" used in the claimed methods are known in the art. (Reply, pp.46+).

Although the instant claims are drawn to methods, the instant claimed methods require the usage of various compounds including "capture compounds", which are drawn to any

compounds as discussed above. In order to demonstrate possession of the instant claimed genus of methods, demonstrate of the compounds used in the methods must also be demonstrated. Without possession of the claimed genus of compounds (including the capture compounds), the instant claimed methods cannot be performed.

As pointed out by applicants, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species or by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F. 3d at 1568, 43 USPQ2d at 1406.

Contrary to applicant's assertion, the instant disclosure does not provide support for the entire genus of claimed compound by providing either common core structure (and/or function) or a number of representative species. The instant claims are drawn to methods of using any "capture compound", which is a required element of the method. The instant claims are broadly drawn to any components that make up the "capture molecules", which can be infinite number of combinations. The instant claims also require each of the components of the "capture molecule" have the appropriate chemistry for the correct functions. It is not known in the art that any chemical can be combined with any other chemical to arrive a capture compound that has the appropriate linker, binding moiety, drug, etc. The few examples listed in the instant specification do not provide either the common structure or the number of representative species for the entire claimed genus.

In addition, case laws have addressed the issues of written description for methods using compounds that are yet to be identified.

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

MPEP 2163. (emphasis added).

In this case, neither the instant specification nor the claims provided the needed structures for the entire claimed genus of compounds. The instant specification at best only describes "a wish or plan for obtaining" the various "capture molecules" that can be used for the claimed methods. Applicant's claimed scope represents only an invitation to experiment regarding possible capture molecules.

Further, merely providing a "laundry list" of species do not convey possession of the entire genus. See MPEP 2163 I:

> "A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967)"

(emphasis added).

Scope of Enablement Rejection

15. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of X, Y, Q and Z substituents like biotin, small molecular weight drugs of known composition, a select number of known "latent" photoactivatable groups like azides, does not reasonably provide enablement for the use of "any" X, Y, Q and Z. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: Applicant's claims are directed to a broad genus of methods for isolating and identifying biomolecules that have been "captured" by a capture compound of formula Q-Z-$(Y/X)_{n/m}$. The Q moiety is described as a sorting function. Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug. X is a ligand to a biomolecule that binds with sufficiently high affinity so that it will be "stable" under mass spectrometric analysis. And Z is moiety for presenting X, Y and Q. Thus, the claims encompass virtually an infinite number of methods employing virtually an infinite number of capture compounds because no structural limitations have been set forth. That is, Applicants have not limited the number of atoms, types of atoms, or the manner is way said atoms can be connected in defining the Q, X, Y and Z moieties. They could be composed of any element in the periodic table. Furthermore, the dependent claims also fail to limit at least one of the X, Y, Z, and Q moieties to anything less than an infinite number of possibilities. Thus, Applicant's claims encompass the entire universe of drugs, drug fragments, drug metabolites, sorting functions, ligands, etc. without exception. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: Furthermore, the predictability in the art is low when the full scope of the claims is taken into consideration. For example, Lauf et al. state, "The preparation of new materials with novel and useful chemical

and/or physical properties is at best unpredictable considering current levels of understanding. Consequently, the discovery of new materials depends largely on the ability to synthesize and analyze new compounds. Given approximately 100 elements in the periodic table, which can be used to make compositions consisting of three, four, five, six or more elements, the universe of possible new compounds remains largely unexplored" (e.g., see U.S. Patent Application Pub. No. 2004/0062911 A1, page 1, paragraph 4). Thus, the presently claimed compounds by analogy "remain largely unexplored" because they could be constructed of any conceivable combination of elements in the periodic table. Furthermore, although organic chemistry (i.e., compounds restricted to a limited number of elements in the periodic table) is a mature art, it is not sufficiently developed to permit the synthesis of any pharmaceutical drug, drug fragment, drug intermediate, drug metabolite, etc. For example, Keaslin et al. state, "many natural products [which would include pharmaceutical drugs, drug fragments, drug intermediates, drug metabolites, etc.] have complex structures, and, as a result, are currently … impossible to synthesize" (e.g., see Keasling et al., US Patent Application No. 2006079476, paragraph 6).

Furthermore, it is unclear how a sufficient time for reaching equilibrium between the biomolecule and the capture compound can be achieved without the use of a photoactivatable X group or, alternatively, an X group that can be activated by a change in pH (see above). Reaching equilibrium takes time and an X group that is constitutively activated would not permit such a waiting period. A constitutively activated X group would react immediately with the target before equilibrium could be achieved between the drug and the biomolecule. Thus, Applicants were not in possession of any X group but, rather, only a select number of "activatable" groups (e.g., see Example 15 wherein a photoactivatable group was used to take a

"snap shot" of the reaction at the time of photolysis).

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants set forth only a handful of examples in their specification that have been used to capture compounds under "equilibrium" conditions. For example Q could be biotin, an oligonucleotide, hex-His, antibody, lectin, PNA, peptide(see specification, page 53, paragraph 1). No entirely "inorganic" Q sorting function is disclosed. X, according to Applicants, could be a photoactivatable group or an activated ester if used under acidic conditions (e.g., see also page 87; see also Example 15; see especially page 197, lines 5-11 describing why photoactivatable groups are required, "The central assumption is that the photolysis process is a very rapid process so that the amount of the covalently crosslinked substrate enzyme complex is directly proportional to the amount of the complex in equilibrium"; see also page 47, last full paragraph wherein an azide is presented; see also page 124, compound A for an example of such an azide; see also page 76, paragraph 1 wherein a diazirine group is disclosed and an NHS group that is "inert" under acidic pH but is subsequently activated at high pH; see also original claims 141 and 142 disclosing arylazides and phenyl azides). Although many other X groups were described in the specification, none were described as being able to capture compounds under "equilibrium" conditions. Several commonly known drugs were described for the "Y" position such as Troglitazone, Rosiglitazone, Pioglitazone (e.g., see prophetic example 16) and atorvastatin calcium i.e., LIPITOR (e.g., see specification page 91). A drug metabolite of Actos and Avandia were also described (e.g., see specification, pages 206 and 207). No example of a drug

"fragment" is provided that could read, quite literally, on a single carbon atom. No example of a "prodrug" is provided. Finally, only multivalent "carbon based" Z presenting units are provided. No inorganic examples are given (e.g., see claim 34).

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Discussion and Answer to Argument

16. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traverse the above Scope of Enablement rejection with similar argument as the traversal over the Written Description Rejection. (Reply, pp.19+).

Applicants are respectfully directed to the discussion under Written Description Rejection for additional comments.

Applicants assert "[T]he claims are not directed to compounds, but are directed to methods… one [compounds] that is selected by a user to be assessed." However, the instant claims are not drawn to a screening method for identifying "a capture compound", where

unknown compounds/molecules are selected. The instant claims are drawn to a method of using "a capture compound" for identifying other targets/non-targets. The requirement under 35 USC 112, 1st paragraph is that "*to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...*" That is one of ordinary skill in the art must be able to make and use the instant claimed invention. In order to use the instant claimed methods, one of skill in the art must also be able to make and use the "capture compounds," which are necessary to perform the claimed methods.

As discussed above (in the body of the rejection), the state of the art demonstrates (see cited references) that it is highly unpredictable to make and use any "capture compound" that are composed of any chemicals (as it is broadly claimed in the instant case).

Applicants cited several references to indicate the "capture compounds" (Reply, p.20, last para) are known in the art. However, applicants also admit that at least capture compounds containing a "Y moiety" and the X (or the combination thereof) are not described in the listed citations. Therefore, applicants have not demonstrated that it is predictable to generate any capture molecule with any substituent groups including the various claimed components such as the Y, X, Z and Q moieties. In other words, one of skill in the art must by trial and error to combine the various components to arrive at a usable "capture moiety" for selection of a target. This trial and error process has not been demonstrated to be predictable and can be done without undue experimentation. For examples, at least the various chemical reactions that might be involved in forming the capture moiety would be highly unpredictable because different chemical subsitutent groups would have different reactivity and compatibility with each other. Neither the art nor the instant specification provides a predictable and/or systemic way of

generating any capture moiety with any chemical compounds.

Applicants also cited a few working examples of the instant specification. However, these working examples only provide a few chemical compounds that have similar structures, which have not been demonstrated to be generalizable to any compound (such as the ones do not share the same core chemical structures).

Claims Rejections - 35 U.S.C. 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158, 159, 160, 163, 164, 166 and 169 are rejected under 35 U.S.C. 102(b) as being anticipated by Hasegawa et al. (Hasegawa et al., "Determination of the Binding Site on the Extracellular Domain of Guanyl Cyclase C to Heat-stable Enterotoxin" *J. Biol. Chem.* **1999**, *274*, 44, 31713-31719) as evidenced by, if necessary, Saeed et al. (WO 2006/138571 A2) (Date of Patent is December 28, 2006) and Samanta et al. (Samanta et al., "Escherichia coli heat stable entertoxin receptors & guanylyl cyclases activity in the intestinal brush border membrane of hamsters & guinea pigs" *Indian Journal of Medicinal Research*, **January 2001**, pages 1-6 downloaded from http://findarticles.com/p/articles/mi_qa3867/is_200101/ai_n8947273/pg_1 on November 12, 2007) and Chao et al. (Chao et al., "Interaction of Escherichia coli Heat-Stable Enterotoxin B

with Cultured Human Intestinal Epithelial Cells" Infection and Immunity **1997**, 65(8), 3209-3217) and Savige et al. (Savige et al., "Cleavage of the Tryptophanyl Peptide Bond by Dimethyl Sulfoxide-Hydroboromic Acid" *Methods in Enzymology*, **1977**, *47*, 459-469) and Kahne et al. (Kahne et al., "Hydrolysis of a Peptide Bond in Neutral Water" *J. Am Chem. Soc.* **1988**, *110*, 7529-7534) and Adams et al. (Adams et al., "A new caged Ca2+, azid-1, is far more photosensitive than nitrobenzyl-based chelators" *Chemistry & Biology* **1997**, *4*, 867-878). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

For ***claims 1*** *and* ***6***, Hasegawa et al. (see entire document) disclose a method for the determination of the binding site on the extracellular domain of guanylyl cyclases c to a heat-stable enterotoxin (e.g., see Hasegawa et al, title and abstract), which anticipates the claimed invention. For example, Hasegawa et al. disclose **(a)** contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules in the sample (e.g., see Experimental Procedures, Photoaffinity Labeling of ECD6H and Isolation of a Photoaffinity Labeled Peptide sections wherein ~ 800 pmol of purified ECD6H biomolecules were mixed with the biotinyl-$(AC_5)_2$-[Gly^4,Pap^{11}]STp(4-17) molecules in the dart for 1 hour and subsequently "captured" by covalent attachment by UV irradiation at 302 nm and Ni^{2+}-chelating affinity chromatography). Hasegawa et al. also disclose a latent reactivity group requiring activation (e.g., see figure 1 wherein the photoactivatable phenyl-N3 group is disclosed; see also page 31715, column 1, paragraph 1). The capture compound is shown schematically in figure 1B. The sorting function Q = biotin-$(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys-; X = phenyl azide (i.e., a group that is selected to covalently bind to biomolecules) with n = 1; Y = Pro-Ala-Cys-Ala-Gly-

Cys; Z = NH-CH(CH_2-)-CO of the Pap group. Please note that other variations are possible. For example, Q could be biotin alone and Z could be $(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys-NH-CH(CH_2-)CO or, alternatively, some small portion. In addition, Hasegawa et al. disclose contacting the capture compound and the biomolecules for a sufficient time for the interaction between them to read equilibrium (e.g., see page 31714, column 2, paragraph 1 wherein the two were mixed for 1 hour before the solution was exposed to UV irradiation; see also figure 2 describing competitive binding curves in the binding equilibrium between ECD6H and biotinyl-$(AC_5)_2$-[Gly^4,Pap^{11}]ST-p(4-17)). Hasegawa et al. do not state that the Pro-Ala-Cys-Ala-Gly-Cys segment is a drug or drug fragment but the Examiner contends that this is an inherent property of the sequence because it is part of the STa enterotoxin (e.g., see Figure 1), which induces diarrhea in mammals including humans. Furthermore, Saeed et al. indicates that STa can be used therapeutically to prevent overdose and drug addiction (e.g., see Saeed et al., Background; see also page 5, last paragraph wherein STa is disclosed; see also page 18, paragraph 2; see also page 24, paragraph 2). In addition, Hasegawa et al. do not explicitly state that the contacting was effected for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium. Hasegawa only mention that the mixture was incubated for 1 hour before photoaffinity labeling (e.g., see Hasegawa et al., page 31713, column 2, paragraph 1) and that several competitive ligand binding assay was performed under equilibrium conditions (e.g., see page 31715, column 2, paragraph 2). However, Samanta et al. disclose maximum binding for STa occurs over a 1 hour period for similar receptor/ligand interactions (e.g., see Samanta et al., page 3, second to last paragraph) and Chao et al. disclose an even shorter time for the structurally related STb reaching equilibrium in only 10 minutes (e.g., see page 3211, column

1, second to last paragraph). Thus, it is reasonable to conclude that the structurally related biotinyl-$(AC_5)_2$-[Gly^4,Pap^{11}]STp(4-17) would also achieve equilibrium in less than or equal to one hour with its target ECD6H. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Hasegawa et al. also disclose **(b)** forming a covalent linkage or high affinity bond between X and the biomolecule to effect capture thereof (e.g., see page 31714, column 2 paragraph 1 wherein the photoaffinity labeling and separation was described; see also page 31715, column 1, paragraph 1, "The synthetic ligand contained two functional residues as follows: one was a photosensitive amino acid (Pap) with azido group, which is easily converted to nitrene by radiation with UV light (300 nm) and covalently anchored to electron-rich groups such as N-H, O-H, etc. on the receptor molecule"). Finally, Hasegawa et al. disclose **(c)** isolating and identifying the captured biomolecules to thereby identify biomolecules that interact with moiety Y (e.g., see Experimental; see also figures 3 and 4 identifying the isolated SPTFIWK sequence).

For ***claim 2***, Hasegawa et al. disclose a non-specific target like Tris (e.g., see page 31714, column 2, paragraph 1). In addition, fragments like PTFI and FIWK were also identified in addition to the SPTFIWK (e.g., see page 31716, column 2, last paragraph).

For ***claim 10***, Hasegawa et al. disclose a Q that permits separation of capture compounds by arraying of the capture compounds on a solid support by binding to the surface of a molecule

thereon (e.g., see page 31714, column 1, paragraph 2 wherein an avidin-immobilized matrix is disclosed for reacting with the biotin labeled Q; see also column 2, paragraph 3; see also page 31714, column 1, paragraph 1; see also column 2, second full paragraph; see also page 31716, column 2, last paragraph).

For ***claim 15***, Hasegawa et al. disclose, as one possibility, a $(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys-NH-CH(CH_2-)CO "Z" moiety wherein any of the peptide bonds are "cleavable" by say a peptidase (i.e., enzymatically cleavable) which could occur before mass spectrometric analysis. Please note that claim 15 does not actually recite a positive method step for performing mass spectroscopy but, rather, merely states that "if" mass spectroscopy were to be performed then the bond could be cleaved.

For ***claim 25***, Hasegawa et al. do not explicitly state that peptide bonds are cleavable by acid but this is an inherent property of a peptide bond as exemplified by Savige et al. and Kahn et al. (e.g., title wherein dimethyl sulfoxides-hydrobromic acid is disclosed; see also page 459-460; see also Kahn et al., figure 2 showing hydrolysis rates from pH –1 to 15).

For ***claim 34***, Hasegawa et al. disclose many possibilities that read on the claimed $(S^1)_tM(R^{15})_a(S^2)_bL$ formula. For example, Z could be NH-CH(CH_2-)-CONH wherein the underlined portion constitutes the "M" group that is that possess three points of attachment to the biotinyl-$(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys- group, phenyl-N3 and CONH groups and t, a and b are all zero. In this scenario, the "L" portion of the molecule is represented by the terminal CONH which can be cleaved by peptidases (e.g., see claim 15 above) or acid (e.g., see claim 25 above).

For ***claim 38***, Hasegawa et al. disclose, for example, an acid/base cleavable group (e.g.,

see Kahne et al., figure 2).

For ***claim 43***, Hasegawa et al. disclose an X that is selected from the group consisting of an active ester, an active halo moiety, an amino acid side chain-specific functional group, and a specific peptide that binds to a biomolecule surfaces (e.g., see Hasegawa et al., figure 1 wherein phenyl-azide is disclosed that reacts with NH and OH amino acids; see also page 31715, column 1, paragraph 1).

For ***claim 75***, Hasegawa et al. disclose Q = biotin (e.g., see figure 1).

For ***claim 110***, Hasegawa et al. disclose identifying or detecting a captured biomolecule by mass spectrometric analysis (e.g., see figure 3).

For ***claim 116***, Hasegawa et al. disclose a biological sample (e.g., see Materials and Methods; see especially "Photoaffinity Labeling of ECD6H with Biotinyl-$(AC_5)_2$-[Gly^4,Pap^{11}]STp(4-17)" section).

For ***claim 137***, Hasegawa et al. disclose Z = $(S^1)_tM(R^{15})_a(S^2)_b$ wherein t, a, and b are zero and M represents, for example, NH-CH(CH_2-)-CO, which is connected to via 3 points of attachment to the biotinyl-$(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys, phenyl-N3, and Pro-Ala-Cys-Ala-Gly-Cys groups. Please note that there are many variations here that read on the claims (see above for some examples).

For ***claim 139***, Hasegawa et al. disclose X = photoactivatable group (e.g., see figure 1 wherein phenyl-N3 is disclosed; see also page 31715, column 1, paragraph 1, "a photosensitive amino acid (Pap) with azido group, which is easily converted to nitrene by radiation with UV light (300 nm) and covalently anchored to electron-rich groups such as N-H, O-H, etc. on the receptor molecule).

For ***claim 140***, Hasegawa et al. disclose that the capture compound interacts with the biomolecule mixture prior to activation of the photoactivatable group (e.g., see page 31714, column 2, paragraph 1 wherein the biomolecules capture compound are allowed to mix for one hour before activation).

For ***claim 144***, Hasegawa et al. disclose further identifying the function of the capture biomolecule (e.g., see figures 4 and 5 and results wherein the binding residues (i.e., a binding motif) was discovered).

For ***claim 151***, Hasegawa et al. disclose that the sample is contacted with a collection of capture compounds (e.g., see page 31714, column 2, paragraph 1 wherein a collection of 100 nmol of capture compounds is disclosed).

For ***claim 152***, Hasegawa et al. disclose that the X moiety of the capture compound comprises an azide which, following activation, reacts with the biomolecule (e.g., see figure 1; see also page 31715, column 2, paragraph 1).

For ***claim 158***, Hasegawa et al. disclose treating the equilibrium mixture to form a covalent bond (e.g., see page 31714, column 2, paragraph 1; see also page 31715, column 1, paragraph 1).

For ***claim 159***, Hasegawa et al. do not disclose that a change in pH accompanies the photoactivation reaction but it is respectfully submitted that this is an inherent property of the reaction as evidenced by Adams et al. (e.g., see Adams et al., figure 4; see also page 874, column 2, first full paragraph indicating that the nitrene generated upon photoactivation is very basic and would react with water to alter the pH).

For ***claim 160***, Hasegawa et al. disclose the use of a plurality of different concentrations

(e.g., see Materials and Methods; see also figure 2).

For ***claims 163-164***, Hasegawa et al. disclose the use of MALDI-TOF (e.g., see figure 3).

For ***claim 166***, Hasegawa et al. disclose the use of sequence alignment (e.g., see figure 4; see also page 31716, column 2, last paragraph, "Moreover, the peptide fragments that are bound to the photoaffinity ligand with the sequence from residue 388 to residue 391 (PTFI) and that from residue 390 to residue 393 (FIWK) were observed by mass spectrometry (Fig 3). These finding strongly suggest that the ligand binds to the amino acids, Phe or Ile, at positions 390 and 391, respectively, which are common [i.e., overlap] in the tree peptide fragments observed by mass spectrometry").

For ***claim 169***, Hasegawa et al. disclose activation with light (e.g., see page 31715, column 1, paragraph 1 wherein 300 nm UV light was used). Hasegawa et al. disclose Y receptor ligand for a guanylylcyclase (e.g., see abstract).

Discussion and Answer to Argument

19. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants argue the cited reference does not teach all elements of the instant claims. (Reply, p.50+).

1.) Applicants assert the Hasegawa reference does not teach "Z" of the capture formula.

As discussed above and previously, the Hasegawa reference teaches a capture compound shown schematically in figure 1B of the reference. The sorting function Q = biotin-$(AC_5)_2$-Gly-

Cys-Cys-Glu-Leu-Cys-Cys-; X = phenyl azide (i.e., a group that is selected to covalently bind to biomolecules) with n = 1; Y = Pro-Ala-Cys-Ala-Gly-Cys; **Z = NH-CH(CH_2-)-CO** of the Pap group. (Please note that other variations are possible. For example, Q could be biotin alone and Z could be $(AC_5)_2$-Gly-Cys-Cys-Glu-Leu-Cys-Cys-NH-CH(CH_2-)CO or, alternatively, some small portion.)

Contrary to applicant's assertion, the reference teaches all elements of the capture compound. Applicants interpret the entire amino acid chain including the Pap compound (from residue Gly to the last Cys residue) as the "drug" or the "Y" group because the disulfide linkage. However, the instant claims do not exclude compounds where the Y and X groups are linked through disulfide bonds. Furthermore, under reduced conditions, the disulfide linkage of the reference's molecule would be removed. The instant specification does not specifically define or limit each of the Q, Z, X, and Y groups to be of any specific chemical structures. Therefore, any chemical compound/group can be Q, Z, X and Y. Applicants have not demonstrated how the chemical compound of the reference is structurally different from the instant claimed compound.

2.) Applicants assert the Hasegawa reference does not disclose a method for identifying drug targets/non-targets. Applicants seem to argue because the target of the Hasegawa reference is previously known, thus the Hasegawa reference does not teach the step of "identifying". However, the instant specification does not specifically define the term "identifying" to mean identify previously unknown compounds. Applicants have also not provided any evidence to show why the enterotoxin or a portion thereof would not be a "drug target" or "non-drug target". Again, the instant specification does not specifically define the said terms to exclude any particular chemical compound. As the identity of the interacting molecule of the Hasegawa

reference is known and also identified using mass spec., the molecule is "identified" according to the broad and reasonable interpretation of the said term.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hasegawa et al. (Hasegawa et al., "Determination of the Binding Site on the Extracellular Domain of Guanyl Cyclase C to Heat-stable Enterotoxin" *J. Biol. Chem.* **1999**, *274*, 44, 31713-31719) in view of Hasegawa et al. II (Hasegawa et al., "Expression and Characterization of the Extracellular Domain of Guanylyl Cyclase C from a Baculovirus and Sf21 Insect Cells" *Protein Expression and Purification* **1999**, *15*, 271-281) as evidenced by, if necessary, Saeed et al. (WO 2006/138571 A2) (Date of Patent is December 28, 2006) and Samanta et al. (Samanta et al., "Escherichia coli heat stable entertoxin receptors & guanylyl cyclases activity in the intestinal

brush border membrane of hamsters & guinea pigs" *Indian Journal of Medicinal Research*, **January 2001**, pages 1-6 downloaded from http://findarticles.com/p/articles/mi_qa3867/is_200101/ai_n8947273/pg_1 on November 12, 2007) and Chao et al. (Chao et al., "Interaction of Escherichia coli Heat-Stable Enterotoxin B with Cultured Human Intestinal Epithelial Cells" Infection and Immunity **1997**, 65(8), 3209-3217) and Savige et al. (Savige et al., "Cleavage of the Tryptophanyl Peptide Bond by Dimethyl Sulfoxide-Hydroboromic Acid" *Methods in Enzymology*, **1977**, *47*, 459-469) and Kahne et al. (Kahne et al., "Hydrolysis of a Peptide Bond in Neutral Water" *J. Am Chem. Soc.* **1988**, *110*, 7529-7534) and Adams et al. (Adams et al., "A new caged Ca2+, azid-1, is far more photosensitive than nitrobenzyl-based chelators" *Chemistry & Biology* **1997**, *4*, 867-878). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

Hasegawa et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158, 159, 160, 163, 164, 166 and 169. *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) ("anticipation is the epitome of obviousness"); see also *In re Skoner*, 517 F.2d 947, 950, 186 USPQ 80, 83 (CCPA 1975); *In re Pearson*, 494 F.2d 1399, 1402, 181 USPQ 641, 644 (CCPA 1974).

The prior art teaching of Hasegawa et al. differ from the claimed invention as follows:

For ***claim 161***, Hasegawa et al. fail to disclose a method that involves determining a

dissociation constant. Hasegawa et al. only determined IC_{50} values (e.g., see page 31715, column 1, paragraph 2).

However, Hasegawa et al. II teach the following limitations that are deficient in Hasegawa et al.:

For ***claim 161***, Hasegawa et al. II (see entire document) teach the use of calculating K_D values to compare in a quantitative fashion the binding affinity of similar peptides (e.g., see abstract; see also Materials and Methods; see also Results).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to calculate the K_D value of the biotinyl-$(AC_5)_2$-[Gly^4,Pap^{11}]STp(4-17) molecule as disclosed by Hasegawa et al. using the method as disclosed by Hasegawa et al. II because K_D values were commonly employed as a tool for characterizing the binding affinity of ligand for a protein target (e.g., see Hasegawa et al. II, abstract). A person of ordinary skill in the art would have been motivated to calculate the K_D because it offers an easy, quantitative method for comparing binding affinities that is universally employed in the field of chemistry/biochemistry. A person of ordinary skill in the art would have reasonably expected to be successful because Hasegawa et al. II shows that K_D values can be calculated for nearly identical peptides toxins against the same GC-C targets (e.g., see abstract; see also Materials and methods).

Discussion and Answer to Argument

23. Applicant's arguments have been fully considered but they are not persuasive for the

following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in italic):

Applicants traversed the above rejection with the same arguments as the traversal over the Hasegawa reference alone. Applicants are respectfully directed to the above rejection over Hasegawa reference alone of answer to arguments.

New Claim Objection(s) / Rejection(s)

Claim Objections

24. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 1 recites "a method for identifying targets and non-targets" and "biomolecules comprise drug targets and non-targets," which seem to require both the target and the non-target. However, the instant claim 2 only recites non-targets, which does not further limit the instant claim 1.

Claim Rejections - 35 USC § 112, first paragraph

New Matter Rejection

25. Claims 1, 2, 6, 10, 15, 25, 34, 38, 43, 75, 110, 116, 137, 139, 140, 144, 151, 152, 158-161, 163, 164, 166 and 169 are rejected under 35 U.S.C. 112, first paragraph, as failing to

comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended as filed on 4/29/09. However, the instant specification does not provide support for the claimed method as recited in claim 1. In particular, the instant specification and claims as originally filed do not disclose methods where both "targets and non-targets of a drug" are identified together through the covalent binding to the capture compound.

If Applicant believes this rejection is in error, applicant must disclose where in the specification support for the entire scope of the amendment(s) and/or new claims can be found. As a result, Claims 1 and its dependent claims represent new matter.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Primary Examiner, AU 1639
7/20/09